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13. ABSTRACT (Maximum 200 words)  <p>The synthesis of a series of diazatrithia-15-crown-5 and diazatrithia-16-crown-5 ligands containing two 8-hydroxyquinoline side arms are reported. The ligands were prepared by a two-step process. First, diazatrithiacrown ethers <b>11</b> and <b>12</b> were prepared by treating bis(<math>\alpha</math>-chloroamide) <b>5</b> with various dimercaptans followed by reduction using a boron-THF complex. Hydroxymethyl-substituted macrocycle <b>12</b> was rearranged to hydroxy-substituted diazatrithia-16-crown-5 in refluxing aqueous HCl. Macrocyclic diamines <b>11-13</b> were converted to either 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted diazatrithiacrown ethers <b>14-16</b> by a Mannich aminomethylation reaction or to 8-hydroxyquinolin-2-ylmethyl-substituted diazatrithiacrown ethers <b>17-19</b> by reductive amination using 8-hydroxyquinoline-2-carboxaldehyde.</p>				
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by

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# Synthesis of Bis-8-Hydroxyquinoline-Armed Diazatrithia-15-Crown-5 and Diazatrithia-16-Crown-5 Ligands

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## Results and Discussion

**Synthesis of Diazatrithia Crown Ethers.** Secondary ring nitrogen atoms in crown ethers offer a convenient site for attachment of alkyl substituents. The crab-like synthesis of diazacrown ethers using the bis( $\alpha$ -chloroacetamide)s provides a relatively high yield method to form macrocycles containing two secondary amine functions.<sup>1b,2</sup> In this regard, bis( $\alpha$ -chloroamide) **5** was treated with various dimercaptans in MeCN using a carbonate base to form macrocyclic diazatrithiadiamides **6-8** in good yields (Scheme 1). As expected, the larger 2:2 cycloaddition products, macrocyclic tetraamides **9** and **10**, were also isolated in two cases in small yields. The NMR spectra of **9** and **10** were similar to those of **6** and **8**, respectively. High dilution techniques helped minimize the production of these undesired by-products. Macrocyclic diazatrithia ligands **11** and **12** were prepared by reducing macrocyclic diamides **6** and **8**, respectively, using a borane-THF complex. Initially, work up of the borane reduction products was done in refluxing 6 M HCl, but this process caused the formation of unexpected rearrangement and ring opened products as discussed below. Exposure to 6 M HCl at room temperature for a period of 10 minutes, along with extraction, was adequate for freeing the desired product from boron giving diazatrithia-18-crown-6 (**11**) and hydroxymethyl-substituted diazatrithia-15-crown-5 (**12**) in good yields.

The rearrangement product of **12** proved to be a new hydroxy-substituted diazatrithia-16-crown-5 (**13**) (Scheme 2). Ligand **13** is also of value in our research program. In an acid environment with heating, the protonated primary hydroxyl group from **12** becomes a leaving group when attacked by the neighboring ring sulfur atom. This leads to a charged epithio intermediate that is in turn attacked by water at the carbon atom most able to support a positive charge, forming **13**. A minor product from this reaction resulted from the intramolecular attack by a neighboring ring nitrogen atom forming **13a** in a very low-yield. A trace amount of another compound which has very similar properties to those of **13a** was also observed. This material could be a result of the attack of the other ring nitrogen atom on the epithio intermediate.

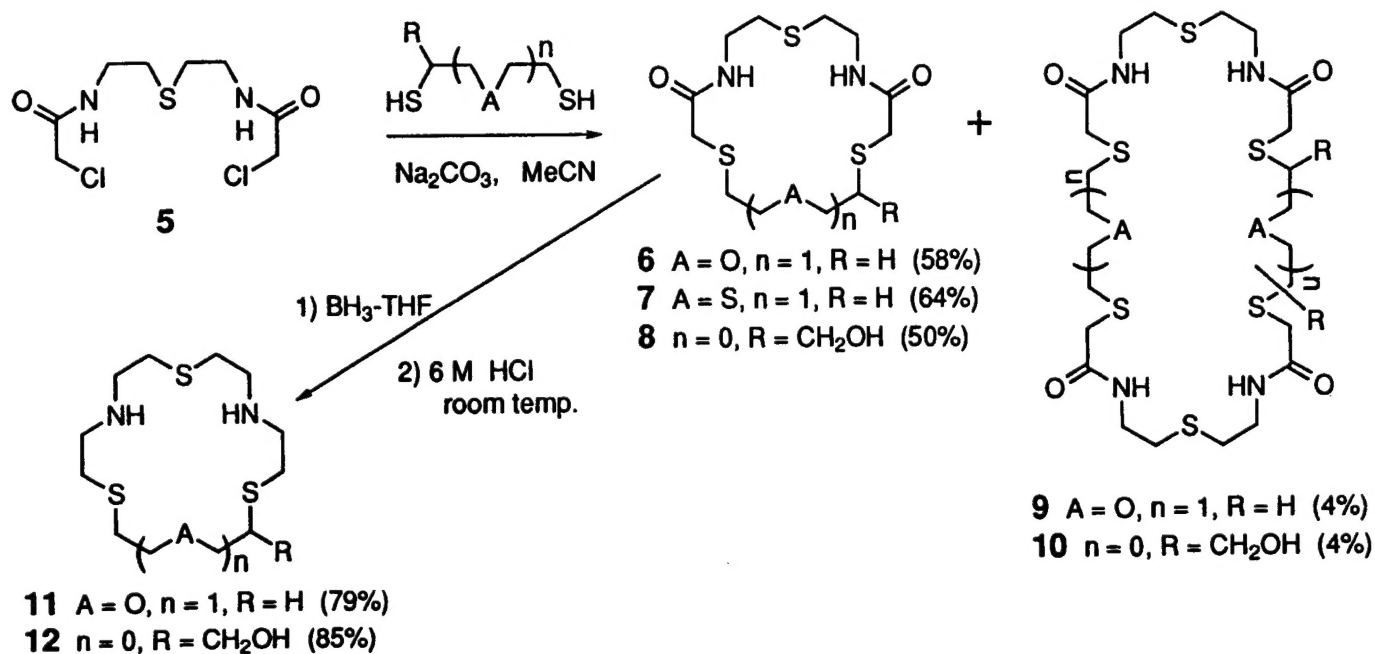
**Synthesis of 8-Hydroxyquinoline-substituted Ligands.** Ligands **14-16** with the CHQ units attached at the CHQ 7-position were formed using Mannich reaction conditions as shown in Scheme 3.<sup>1d,3</sup> The best results were achieved by first forming the *N,N'*-bis(methoxymethyl)diazacrown ethers by stirring the diaza crowns in methanol and a slight excess of paraformaldehyde.<sup>3</sup> After removal of methanol and addition of benzene to the mixtures, CHQ was added and the mixtures were refluxed. Benzene

proved to be a good reaction solvent since there were few side products. Products **14-16** were purified using radial chromatography.

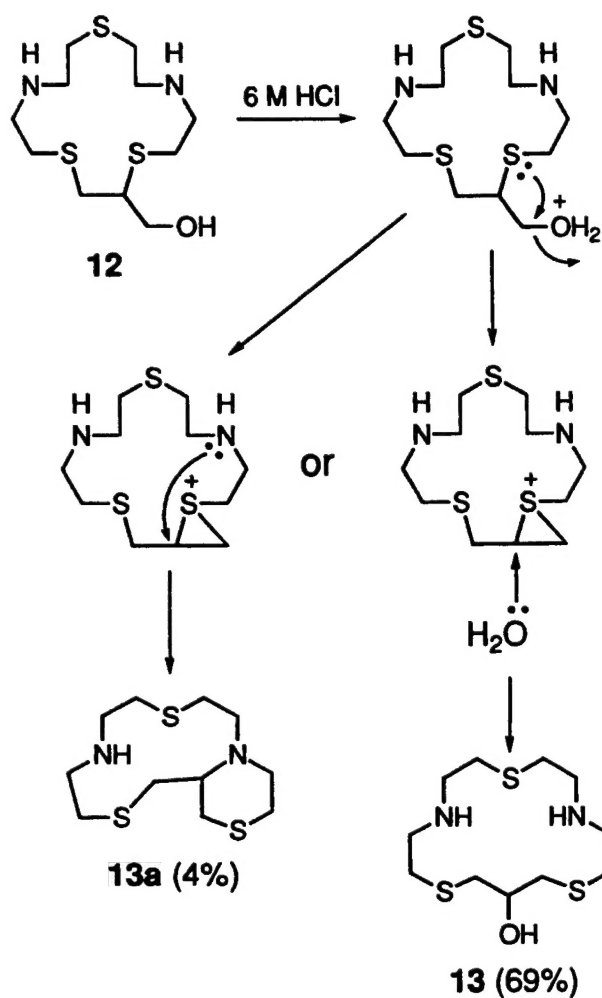
Compounds **17-19** (Scheme 4) were obtained in good yields using a reductive amination procedure.<sup>1a,1b</sup> Ligands **17-19** with the 8-hydroxyquinoline side arms attached at their 2-positions were more readily isolated than compounds **14-16** with CHQ units attached at their 7-positions.

## References

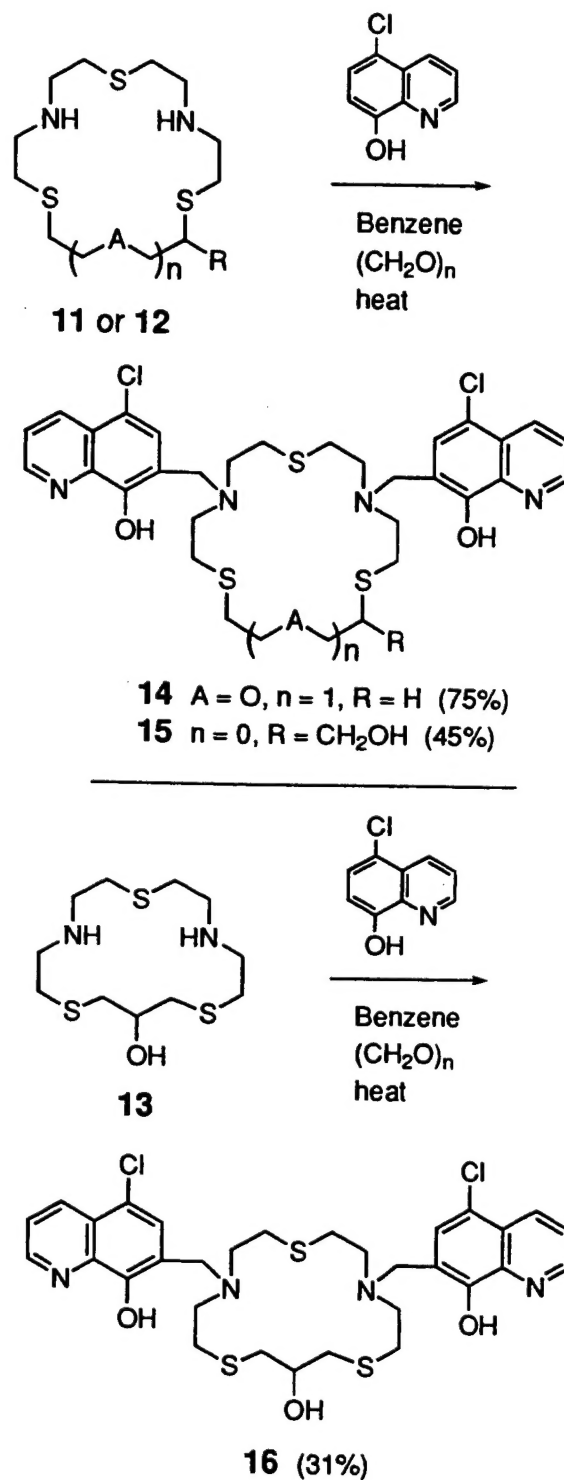
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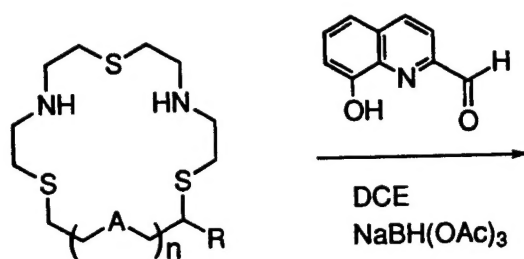
Scheme 1. Syntheses of diazatrithiacrown ethers **11** and **12** containing two unsubstituted nitrogen atoms



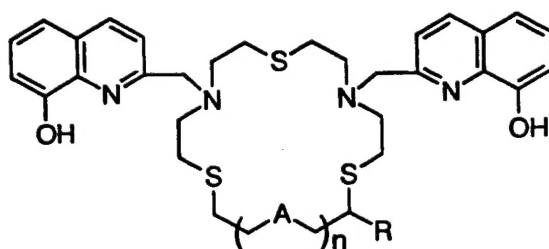
Scheme 2. Rearranged crown ethers **13** and **13a**



Scheme 3. Syntheses of 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted crown ethers via the Mannich reaction

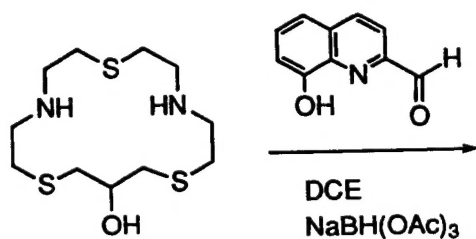


**11 or 12**

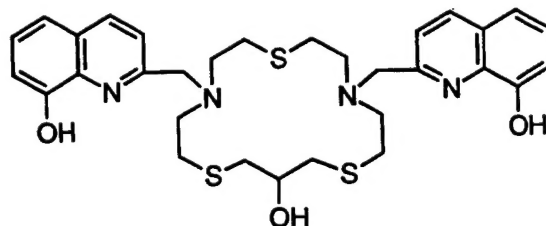


**17** A = O, n = 1, R = H (75%)

**18** n = 0, R = CH<sub>2</sub>OH (69%)



**13**



**19** (64%)

Scheme 4. Syntheses of 8-hydroxy-quinolin-2-ylmethyl-substituted crown ethers via reductive amination